

Many Genes Involved in Tourette Syndrome Pathogenesis

Willsey AJ, Fernandez TV, Yu D, et al. De novo coding variants are strongly associated with Tourette disorder. *Neuron* 2017;94:486-499.

Despite considerable efforts, genetic studies of Tourette syndrome (TS) have not been very productive. The analyses of some unusual pedigrees identified possible risk genes, but larger scale linkage and association studies were fruitless. Using advanced conceptual and technological tools, Willsey and colleagues¹ present compelling evidence for involvement of multiple genes in TS. They studied parent-child trios with an affected child and unaffected parents. Genomes were analyzed with whole exome sequencing to identify de novo variants potentially associated with TS. An excess of likely gene disrupting variants (premature stop codons, frameshift variants, splice-site variants), and likely damaging missense variants was observed in TS trios. Using statistical simulation methods, Willsey and colleagues¹ extrapolated that there are in excess of 400 TS risk genes. Based on the presence of recurrent de novo variants, Willsey and colleagues¹ identified 4 candidate TS risk genes.

This study demonstrates both the strengths and weaknesses of genetic approaches to neurodevelopmental disorders. The results are potentially fruitful, but this work may be motivated by a misconception. The authors state that they are pursuing novel therapeutic targets by seeking to understand TS pathophysiology. This is incorrect. The authors are studying pathogenesis by attempting to isolate etiologic factors. It is likely that many of the likely gene-disrupting, variant-carrying genes identified play roles in

brain development. Data about the 4 identified candidate TS risk genes are consistent with this inference.

There is a good likelihood that Willsey and colleagues¹ identified mutations causing an emergence of abnormal circuits underlying clinical phenomena such as tics and comorbid behavioral disorders common in TS. Understanding the normal functions of these genes and the consequences of these mutations will be informative about brain development. This knowledge, however, is less likely to be informative about the abnormal physiology of aberrant circuits. Understanding the latter is what is indispensable for developing novel treatments. This is important work, but its major impact will probably be in the domain of developmental neurobiology. ■

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Reference

1. Willsey AJ, Fernandez TV, Yu D, et al. De novo coding variants are strongly associated with Tourette disorder. *Neuron* 2017;94:486-499.

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